



## Clinical trial results:

### A Phase 3, 2-Part, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis (CF) Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Ivacaftor-responsive CFTR Mutation

#### Summary

EudraCT number	2015-001997-16
Trial protocol	GB IE DE
Global end of trial date	28 June 2022

#### Results information

Result version number	v1 (current)
This version publication date	21 June 2023
First version publication date	21 June 2023

#### Trial information

##### Trial identification

Sponsor protocol code	VX15-770-124
-----------------------	--------------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02725567
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States,
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000335-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 June 2022
Global end of trial reached?	Yes
Global end of trial date	28 June 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety, pharmacokinetics (PK), and pharmacodynamics of ivacaftor in subjects with CF who are less than (<) 24 months of age and have an ivacaftor-responsive CFTR mutation.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Ireland: 5
Worldwide total number of subjects	57
EEA total number of subjects	5

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	57
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0
-------------------	---

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

This study was conducted in subjects with cystic fibrosis (CF) who were less than (<) 24 months of age at Day 1 and have an ivacaftor-responsive CF transmembrane conductance regulator (CFTR) mutation.

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	Part A: 3 to < 24 months

Arm description:

Subjects weighing 5 to less than (<) 7 kilogram (kg) received 25 milligram (mg) IVA (ivacaftor), 7 to <14 kg received 50 mg IVA, and those weighing 14 to <25 kg received 75 mg IVA administered every 12 hours (q12h) on Days 1 through 3 and 1 morning dose on Day 4.

Arm type	Experimental
Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	Ivacaftor
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA dose every 12 hours.

<b>Arm title</b>	Part B + A/B: 1 to <24 months
------------------	-------------------------------

Arm description:

Subjects 4 to <6 months of age and weighing greater than or equal to ( $\geq$ ) 5 kg received 25 mg IVA q12h. At 6 months of age and older, participants weighing 5 to <7 kg received 25 mg IVA, 7 to <14 kg received 50 mg IVA, and those weighing 14 to <25 kg received 75 mg IVA q12h for 24 weeks on Part B.

For Part A/B, subjects 1 to <4 months weighing 3 kg to <5 kg received an initial low dose of 5.7 mg q12h IVA and those weighing  $\geq$ 5 kg received 11.4 mg q12h IVA for the first 15 days of IVA treatment. Doses were maintained or adjusted upward at Day 15 and based on weight and/or age once they reached 4 months of age.

Arm type	Experimental
Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	Ivacaftor
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA dose every 12 hours.

<b>Number of subjects in period 1</b>	Part A: 3 to < 24 months	Part B + A/B: 1 to <24 months
Started	19	43
Completed	19	40
Not completed	0	3
Physician decision	-	1
Lost to follow-up	-	1
Withdrawal of Consent (not due to AE)	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Part A: 3 to < 24 months
-----------------------	--------------------------

Reporting group description:

Subjects weighing 5 to less than (<) 7 kilogram (kg) received 25 milligram (mg) IVA (ivacaftor), 7 to <14 kg received 50 mg IVA, and those weighing 14 to <25 kg received 75 mg IVA administered every 12 hours (q12h) on Days 1 through 3 and 1 morning dose on Day 4.

Reporting group title	Part B + A/B: 1 to <24 months
-----------------------	-------------------------------

Reporting group description:

Subjects 4 to <6 months of age and weighing greater than or equal to ( $\geq$ ) 5 kg received 25 mg IVA q12h. At 6 months of age and older, participants weighing 5 to <7 kg received 25 mg IVA, 7 to <14 kg received 50 mg IVA, and those weighing 14 to <25 kg received 75 mg IVA q12h for 24 weeks on Part B.

For Part A/B, subjects 1 to <4 months weighing 3 kg to <5 kg received an initial low dose of 5.7 mg q12h IVA and those weighing  $\geq$ 5 kg received 11.4 mg q12h IVA for the first 15 days of IVA treatment. Doses were maintained or adjusted upward at Day 15 and based on weight and/or age once they reached 4 months of age.

Reporting group values	Part A: 3 to < 24 months	Part B + A/B: 1 to <24 months	Total
Number of subjects	19	43	62
Age categorical			
Units: Subjects			

Age continuous			
There were 57 unique subjects enrolled in the study. Out of 19 subjects from Part A, 5 subjects also participated in Part B.			
Units: months			
arithmetic mean	10.8	9.5	
standard deviation	$\pm$ 7.18	$\pm$ 5.93	-
Gender categorical			
There were 57 unique subjects enrolled in the study. Out of 19 subjects from Part A, 5 subjects also participated in Part B. The total column for gender represents the sum of Part A, Part B + A/B numbers as the data for unique 57 subjects was not collected separately.			
Units: Subjects			
Female	10	22	32
Male	9	21	30
Ethnicity			
There were 57 unique subjects enrolled in the study. Out of 19 subjects from Part A, 5 subjects also participated in Part B.			
Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	19	42	56
Not collected per local regulations	0	0	0
Race			
There were 57 unique subjects enrolled in the study. Out of 19 subjects from Part A, 5 subjects also participated in Part B.			
Units: Subjects			
White	19	43	57
Black or African American	0	0	0
Asian	0	0	0
American Indian or Alaska Native	0	0	0

Native Hawaiian or Other Pacific Islander	0	0	0
Not collected per local Regulations	0	0	0

---

## End points

### End points reporting groups

Reporting group title	Part A: 3 to < 24 months
-----------------------	--------------------------

Reporting group description:

Subjects weighing 5 to less than (<) 7 kilogram (kg) received 25 milligram (mg) IVA (ivacaftor), 7 to <14 kg received 50 mg IVA, and those weighing 14 to <25 kg received 75 mg IVA administered every 12 hours (q12h) on Days 1 through 3 and 1 morning dose on Day 4.

Reporting group title	Part B + A/B: 1 to <24 months
-----------------------	-------------------------------

Reporting group description:

Subjects 4 to <6 months of age and weighing greater than or equal to ( $\geq$ ) 5 kg received 25 mg IVA q12h. At 6 months of age and older, participants weighing 5 to <7 kg received 25 mg IVA, 7 to <14 kg received 50 mg IVA, and those weighing 14 to <25 kg received 75 mg IVA q12h for 24 weeks on Part B.

For Part A/B, subjects 1 to <4 months weighing 3 kg to <5 kg received an initial low dose of 5.7 mg q12h IVA and those weighing  $\geq$ 5 kg received 11.4 mg q12h IVA for the first 15 days of IVA treatment. Doses were maintained or adjusted upward at Day 15 and based on weight and/or age once they reached 4 months of age.

Subject analysis set title	Part A/B: 1 to <4 months
----------------------------	--------------------------

Subject analysis set type	Full analysis
---------------------------	---------------

Subject analysis set description:

Subjects 1 to <4 months weighing 3 kg to <5 kg received an initial low dose of 5.7 mg q12h IVA and those weighing  $\geq$ 5 kg received 11.4 mg q12h IVA for the first 15 days of IVA treatment. Doses were maintained or adjusted upward at Day 15 and based on weight and/or age once they reached 4 months of age.

Subject analysis set title	Part B: 4 to <24 months
----------------------------	-------------------------

Subject analysis set type	Full analysis
---------------------------	---------------

Subject analysis set description:

Subjects 4 to <6 months of age and  $\geq$ 5 kg received 25 mg IVA q12h. At 6 months of age and older, subjects weighing 5 to <7 kg received 25 mg IVA, 7 to <14 kg received 50 mg IVA, and those weighing 14 to <25 kg received 75 mg IVA q12h for 24 weeks on Part B.

### Primary: Part A : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious (TEAEs)

End point title	Part A : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious (TEAEs) <sup>[1][2]</sup>
-----------------	---

End point description:

Safety Set included all subjects who received at least 1 dose of study drug.

End point type	Primary
----------------	---------

End point timeframe:

Day 1 through Day 70

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were planned. No statistical comparisons were planned for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This end point is only applicable for Part A.



<b>End point values</b>	Part A: 3 to < 24 months			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Subjects				
Subjects with TEAEs	10			
Subjects with Serious TEAEs	1			

## Statistical analyses

No statistical analyses for this end point

## Primary: Part A: Observed Plasma Concentration of IVA and Their Metabolites (M1-IVA and M6-IVA)

End point title	Part A: Observed Plasma Concentration of IVA and Their Metabolites (M1-IVA and M6-IVA) <sup>[3][4]</sup>
-----------------	--

End point description:

PK set included subjects who received at least 1 dose of study drug. Here the "n" signifies those subjects who were evaluable at specified time point.

End point type	Primary
----------------	---------

End point timeframe:

Pre-dose, 2-4 hours, 6-8 hours, 24-60 hours post-dose

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were planned. No statistical comparisons were planned for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This end point is only applicable for Part A.

<b>End point values</b>	Part A: 3 to < 24 months			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: nanogram per millilitre (ng/ml)				
arithmetic mean (standard deviation)				
Pre dose: IVA (n=19)	654 (± 531)			
Pre dose: M1-IVA (n=19)	1880 (± 1160)			
Pre dose: M6-IVA (n=19)	2680 (± 1990)			
2-4 hrs post dose: IVA (n=19)	956 (± 497)			
2-4 hrs post dose: M1-IVA (n=19)	1990 (± 1160)			
2-4 hrs post dose: M6-IVA (n=19)	2460 (± 2110)			
6-8 hrs post dose: IVA (n=19)	1040 (± 623)			
6-8 hrs post dose: M1-IVA (n=19)	2440 (± 1260)			
6-8 hrs post dose: M6-IVA (n=19)	2880 (± 2180)			
24-60 hrs post dose: IVA (n=18)	129 (± 68.8)			
24-60 hrs post dose: M1-IVA (n=18)	508 (± 228)			
24-60 hrs post dose: M6-IVA (n=18)	1100 (± 982)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Part B + Part A/B: Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious (TEAEs)

End point title	Part B + Part A/B: Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious (TEAEs) <sup>[5][6]</sup>
-----------------	---

End point description:

Safety Set included all subjects who received at least 1 dose of study drug.

End point type	Primary
----------------	---------

End point timeframe:

Day 1 through Week 38

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were planned. No statistical comparisons were planned for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This end point is only applicable for Part B + A/B.

<b>End point values</b>	Part B + A/B: 1 to <24 months			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Subjects				
Subjects with TEAEs	38			
Subjects with Serious TEAEs	6			

## Statistical analyses

No statistical analyses for this end point

### Primary: Part A/B: Observed Plasma Concentration of IVA and Their Metabolites (M1-IVA and M6-IVA)

End point title	Part A/B: Observed Plasma Concentration of IVA and Their Metabolites (M1-IVA and M6-IVA) <sup>[7]</sup>
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Day 4 (pre-dose, 2-4 hours, 6-8 hours post-dose); Day 15 (pre-dose); Week 4 (pre-dose); Week 8 (pre-dose, 2-4 hours, 6-8 hours post-dose); Week 12 (pre-dose); Week 18 (pre-dose) and Week 24 (pre-dose)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were planned. No statistical comparisons were planned for this endpoint

End point values	Part A/B: 1 to <4 months			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ng/ml				
arithmetic mean (standard deviation)				
Day 4 (pre dose): IVA (n=7)	348 (± 151)			
Day 4 (pre dose): M1-IVA (n=7)	867 (± 412)			
Day 4 (pre dose): M6-IVA (n=7)	1570 (± 570)			
Day 4 (2-4 hrs post dose): IVA (n=7)	381 (± 135)			
Day 4 (2-4 hrs post dose): M1-IVA (n=7)	851 (± 333)			
Day 4 (2-4 hrs post dose): M6-IVA (n=7)	1370 (± 450)			
Day 4 (6-8 hrs post dose): IVA (n=7)	501 (± 196)			
Day 4 (6-8 hrs post dose): M1-IVA (n=7)	1190 (± 420)			
Day 4 (6-8 hrs post dose): M6-IVA (n=7)	1670 (± 551)			
Day 15 (pre dose): IVA (n=6)	191 (± 134)			
Day 15 (pre dose): M1-IVA (n=6)	614 (± 378)			
Day 15 (pre dose): M6-IVA (n=6)	1510 (± 1110)			
Week 4 (pre dose): IVA (n=6)	316 (± 130)			
Week 4 (pre dose): M1-IVA (n=6)	1170 (± 577)			
Week 4 (pre dose): M6-IVA (n=6)	3370 (± 2330)			
Week 8 (pre dose): IVA (n=7)	449 (± 352)			
Week 8 (pre dose): M1-IVA (n=7)	1030 (± 476)			
Week 8 (pre dose): M6-IVA (n=7)	2380 (± 1500)			
Week 8 (2-4 hrs post dose): IVA (n=7)	523 (± 262)			
Week 8 (2-4 hrs post dose): M1-IVA (n=7)	1360 (± 982)			
Week 8 (2-4 hrs post dose): M6-IVA (n=7)	2100 (± 1540)			
Week 8 (6-8 hrs post dose): IVA (n=7)	438 (± 79.8)			
Week 8 (6-8 hrs post dose): M1-IVA (n=7)	1420 (± 606)			
Week 8 (6-8 hrs post dose): M6-IVA (n=7)	2320 (± 1330)			
Week 12 (pre dose): IVA (n=5)	213 (± 173)			
Week 12 (pre dose): M1-IVA (n=5)	906 (± 660)			
Week 12 (pre dose): M6-IVA (n=5)	2500 (± 1760)			
Week 18 (pre dose): IVA (n=6)	226 (± 153)			
Week 18 (pre dose): M1-IVA (n=6)	815 (± 470)			
Week 18 (pre dose): M6-IVA (n=6)	2060 (± 1190)			
Week 24 (pre dose): IVA (n=6)	276 (± 137)			
Week 24 (pre dose): M1-IVA (n=6)	1120 (± 496)			
Week 24 (pre dose): M6-IVA (n=6)	2380 (± 799)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Observed Plasma Concentration of IVA and Their Metabolites (M1-IVA and M6-IVA)

End point title	Part B: Observed Plasma Concentration of IVA and Their Metabolites (M1-IVA and M6-IVA)
End point description:	
PK set included subjects who received at least 1 dose of study drug. Here the "n" signifies those subjects who were evaluable at specified time point.	
End point type	Secondary
End point timeframe:	
Week 2 (pre-dose, 2-4 hours, 6-8 hours post-dose); Week 8 (pre-dose,1 hour, 4 hour post-dose); Week 24 (pre-dose, 2-4 hours post dose)	

End point values	Part B: 4 to <24 months			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: ng/ml				
arithmetic mean (standard deviation)				
Week 2 (pre dose): IVA (n=34)	457 (± 441)			
Week 2 (pre dose): M1-IVA (n=34)	1340 (± 934)			
Week 2 (pre dose): M6-IVA (n=34)	1980 (± 1790)			
Week 2 (2-4 hrs post dose): IVA (n=34)	812 (± 726)			
Week 2 (2-4 hrs post dose): M1-IVA (n=34)	1560 (± 1190)			
Week 2 (2-4 hrs post dose): M6-IVA (n=34)	1770 (± 1970)			
Week 2 (6-8 hrs post dose): IVA (n=32)	969 (± 705)			
Week 2 (6-8 hrs post dose): M1-IVA (n=32)	2210 (± 1360)			
Week 2 (6-8 hrs post dose): M6-IVA (n=32)	2140 (± 1880)			
Week 8 (pre dose): IVA (n=34)	404 (± 376)			
Week 8 (pre dose): M1-IVA (n=34)	1220 (± 782)			
Week 8 (pre dose): M6-IVA (n=34)	1720 (± 1110)			
Week 8 (1 hrs post dose): IVA (n=33)	466 (± 384)			
Week 8 (1 hrs post dose): M1-IVA (n=33)	1100 (± 670)			
Week 8 (1 hrs post dose): M6-IVA (n=33)	1500 (± 881)			
Week 8 (4 hrs post dose): IVA (n=33)	996 (± 520)			

Week 8 (4 hrs post dose): M1-IVA (n=33)	2130 (± 950)			
Week 8 (4 hrs post dose): M6-IVA (n=33)	1750 (± 1010)			
Week 24 (pre dose): IVA (n=35)	301 (± 204)			
Week 24 (pre dose): M1-IVA (n=35)	1050 (± 492)			
Week 24 (pre dose): M6-IVA (n=35)	1600 (± 783)			
Week 24 (2-4 hrs post dose): IVA (n=34)	794 (± 480)			
Week 24 (2-4 hrs post dose): M1-IVA (n=34)	1540 (± 783)			
Week 24 (2-4 hrs post dose): M6-IVA (n=34)	1320 (± 592)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B + Part A/B: Absolute Change in Sweat Chloride

End point title	Part B + Part A/B: Absolute Change in Sweat Chloride <sup>[8]</sup>
End point description:	Sweat samples were collected using an approved collection device.
End point type	Secondary
End point timeframe:	From Baseline at Week 24

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This end point is only applicable for Part B + A/B.

<b>End point values</b>	Part B + A/B: 1 to <24 months			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: millimole per liter (mmol/L)				
arithmetic mean (standard deviation)	-62.0 (± 22.2)			

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Day 1 Through Safety Follow-up Period (up to Day 70 for Part A and up to Week 38 for Part B + A/B)

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

### Reporting groups

Reporting group title	Part A
-----------------------	--------

Reporting group description:

Subjects weighing 5 to <7 kg received 25 mg IVA, 7 to <14 kg received 50 mg IVA, and those weighing 14 to < 25 kg received 75 mg IVA q12h on Days 1 through 3 and 1 morning dose on Day 4.

Reporting group title	Part B + A/B
-----------------------	--------------

Reporting group description:

Subjects 4 to <6 months of age and weighing ≥5 kg received 25 mg IVA q12h. At 6 months of age and older, participants weighing 5 to <7 kg received 25 mg IVA, 7 to <14 kg received 50 mg IVA, and those weighing 14 to <25 kg received 75 mg IVA q12h for 24 weeks on Part B.

For Part A/B, subjects 1 to <4 months weighing 3 kg to <5 kg received an initial low dose of 5.7 mg q12h IVA and those weighing ≥5 kg received 11.4 mg q12h IVA for the first 15 days of IVA treatment. Doses were maintained or adjusted upward at Day 15 and based on weight and/or age once they reached 4 months of age.

Serious adverse events	Part A	Part B + A/B	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	6 / 43 (13.95%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 19 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Distal intestinal obstruction syndrome			

subjects affected / exposed	0 / 19 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 19 (0.00%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema Coxsackium			
subjects affected / exposed	0 / 19 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema herpeticum			
subjects affected / exposed	0 / 19 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 19 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part A	Part B + A/B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 19 (52.63%)	34 / 43 (79.07%)	
Investigations			
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	3 / 43 (6.98%) 4	
Blood pressure increased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	3 / 43 (6.98%) 3	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	7 / 43 (16.28%) 10	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	8 / 43 (18.60%) 8	
Pseudomonas test positive subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	3 / 43 (6.98%) 3	
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 43 (0.00%) 0	
Head injury subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 43 (0.00%) 0	
Vascular disorders Flushing subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 43 (0.00%) 0	
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 43 (0.00%) 0	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 43 (0.00%) 0	
Pyrexia			



subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	12 / 43 (27.91%) 15	
Gastrointestinal disorders			
Teething			
subjects affected / exposed	2 / 19 (10.53%)	2 / 43 (4.65%)	
occurrences (all)	2	2	
Infantile spitting up			
subjects affected / exposed	1 / 19 (5.26%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	0 / 19 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	1 / 19 (5.26%)	6 / 43 (13.95%)	
occurrences (all)	1	8	
Vomiting			
subjects affected / exposed	1 / 19 (5.26%)	8 / 43 (18.60%)	
occurrences (all)	1	9	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 19 (21.05%)	24 / 43 (55.81%)	
occurrences (all)	5	40	
Nasal congestion			
subjects affected / exposed	1 / 19 (5.26%)	6 / 43 (13.95%)	
occurrences (all)	1	9	
Rhinorrhoea			
subjects affected / exposed	1 / 19 (5.26%)	12 / 43 (27.91%)	
occurrences (all)	1	14	
Wheezing			
subjects affected / exposed	1 / 19 (5.26%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Miliaria			
subjects affected / exposed	1 / 19 (5.26%)	2 / 43 (4.65%)	
occurrences (all)	1	3	
Eczema			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	1 / 43 (2.33%) 1	
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 43 (0.00%) 0	
Infections and infestations Hand-foot-and-mouth disease subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	3 / 43 (6.98%) 3	
Ear infection subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	3 / 43 (6.98%) 7	
Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	2 / 43 (4.65%) 2	
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 43 (0.00%) 0	
Otitis media subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	6 / 43 (13.95%) 8	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	7 / 43 (16.28%) 9	
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	3 / 43 (6.98%) 3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2017	Amended to add an interim analysis (IA) of safety, PK, and PD data from subjects in Cohorts 1 and 5 after a sufficient number of subjects in Cohort 5 have completed either their Week 12 or Week 24 Visit. Additional IAs for regulatory or operational purposes may also be performed. Added inclusion criterion that the subject's weight at screening must be within the weight limits as defined for the study drug dose levels. Clarified lower and upper weight limits and added weight limits based on study drug dose levels.
09 June 2020	Amended to added Part A/B Cohort 8 to study subjects 1 to <4 months of age for 24 weeks. Reduced number of subjects in Part A from 20 to 15 subjects and removed minimum of 5 subjects in Cohort 4 because that age range is included in Part A/B Cohort 8. Part A/B Cohort 8 will be conducted sequentially with no treatment gap. Dosing will be initiated with either a 5.7 mg or 11.4 mg dose depending on age and weight at day 1 and adjusted (if necessary) on day 15 based on PK data collected on day 4.
29 June 2020	Clarified strengths and route of administration within Investigational Drug Section of Synopsis.

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported